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Pathogenetic Role of Coronavirus Infection in the Development of Acute Kidney Injury

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Abstract This review summarizes the results of major clinical and experimental studies on the role of coronavirus infection in the development of kidney damage and available in the databases www.elibrary.ru, www.cyberleninka.ru, and the Google Scholar search engine.

Keywords COVID-19, SARS-CoV-2, Acute kidney injury, Chronic kidney disease, Kidney damage, Pathogenesis, Nephropathy, Comorbidity

1. Introduction

Although coronavirus infectious disease (COVID-19) is primarily a respiratory disease, the kidney may be among the target organs of infection with severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Data on the kidney involvement of COVID-19 patients are still very scarce.

However, as more patients are infected worldwide, our understanding of the disease is rapidly evolving [15].

Acute kidney injury (AKI) is one of the complications of COVID-19 that determines the prognosis of the disease. The first studies conducted in China showed the frequency of detection of AKI in adult patients before 29% [3] [6] [7] [16]. The incidence of AKI in the general population is continuously increasing and reaches 0.25%, which is comparable to the incidence of acute myocardial infarction. Despite the continuous improvement of therapeutic technologies, primarily methods of renal replacement therapy, there is no significant improvement in the results of AKI treatment. The outcomes of severe AKI variants remain unsatisfactory, and their mortality rate can reach 70% or more [29].

According to I. Cheruiyot et al., obtained as a result of a study in 2020, AKI is associated with a worse prognosis [4]. E.S. Stolyarevich et al. in 2020 conducted clinical and morphological comparisons of the manifestations of renal pathology in 220 adult patients who died from COVID-19 [30]. The morphological substrate of AKI in most cases was acute damage to the tubular epithelium, venous fullness of the organ (in more than half of the patients), as well as the presence of thrombotic microangiopathies. Many authors emphasize that COVID-19 infection can complicate treatment, care and increase mortality in people with underlying kidney disease [7] [16] [20].

Several studies have shown that the development of AKI in COVID-19 is associated with a high risk of death [5] [6] [9]. However, contradictory data are provided on the frequency of AKI, which varied from 0.5 to 37% in different studies [5] [14] [18]. J. Hirsh et al. Signs of AKI were detected in 36.6% of hospitalized patients with COVID and in 89.7% of patients on artificial lung ventilation (ventilator) [9]. In another study, AKI was observed in 27% of hospitalized patients with COVID-19 and was more common in elderly people with concomitant diseases – arterial hypertension and heart failure [5]. However, in some studies, the incidence of AKI in patients with COVID-19 was significantly lower. For example, L. Wang et al. Renal dysfunction was not detected in 116 hospitalized patients [19]. According to a large Chinese national study based on clinical data from 552 hospitals in 30 provinces, autonomous regions and municipalities (n=1099), AKI develops in 0.5% of patients with confirmed COVID-19. It should be noted that this study included patients younger than 60 years old, and most of them had a mild course of the disease [6].

Several pathogenic mechanisms have been implicated, including critical hypoxia, infammation and sepsis, haemodynamic changes, acute cardiorenal syndrome, rhabdomyolysis, mitochondrial injury, endothelial dysfunction, microembolism, kidney infarction and use of nephrotoxic drugs [11] [15].

Analysis of existing publications showed that older patients and patients with comorbid backgrounds lead the risk group for COVID-19, and the risk of mortality can reach 20% [28]. In such patients, the acquired immune response may be weakened and increasingly compensated by an innate immune response, which leads not only to the elimination of the virus, but also to extensive tissue damage due to the development of a cytokine storm, accompanied by acute

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respiratory distress syndrome. Cases of COVID-19 infection are more common among patients with aggravated somatic status: cardiovascular disorder and diabetes mellitus [21].

According to an analysis of more than 70,000 cases of COVID-19 registered in Wuhan, mild infection was observed in 81% of patients, severe in 14% and extremely severe (respiratory failure, multiple organ failure and/or septic shock) in 5% [2] [25]. Overall, the mortality rate for patients with confirmed SARS-CoV-2 infection was 2.3%, but it was significantly higher among older people (8.0% aged 70-79 years and 14.8% aged ≥80 years) and especially among patients who were in critical condition (49.0%). Higher lethality was also found in the presence of cardiovascular diseases (10.5%), diabetes mellitus (7.3%), chronic lung diseases (6.3%), arterial hypertension (6.0%) and malignant neoplasms (5.6%).

2. Materials and Methods

For the study the role of the new coronavirus infection in the development of acute kidney injury, we studied 58, 30 sources of them included in this review. The keywords were "Acute kidney injury", "Chronic kidney disease", "COVID-19", "SARSCOV-2".

3. Results

The Extent of Kidney Injury in COVID-19

The pathophysiological mechanisms leading to acute kidney injury (AKI) during COVID-19 infection are unclear, but may be due to the effects on renal tubules and endothelial cells that occur during cytokine storm and subsequent damage to the microvasculature as a result of disturbances in the system of blood clotting (Fig. 1) [12] [17].

Pathophysiological Mechanisms

Pathophysiological mechanisms, leading to acute kidney injury (AKI) during COVID-19 infection are not clear, but may be due to the effects on renal tubules and endothelial cells that occur during cytokine storm and, as a consequence, damage to the microvasculature as a result of disturbances in the system of blood coagulation [24] [25].

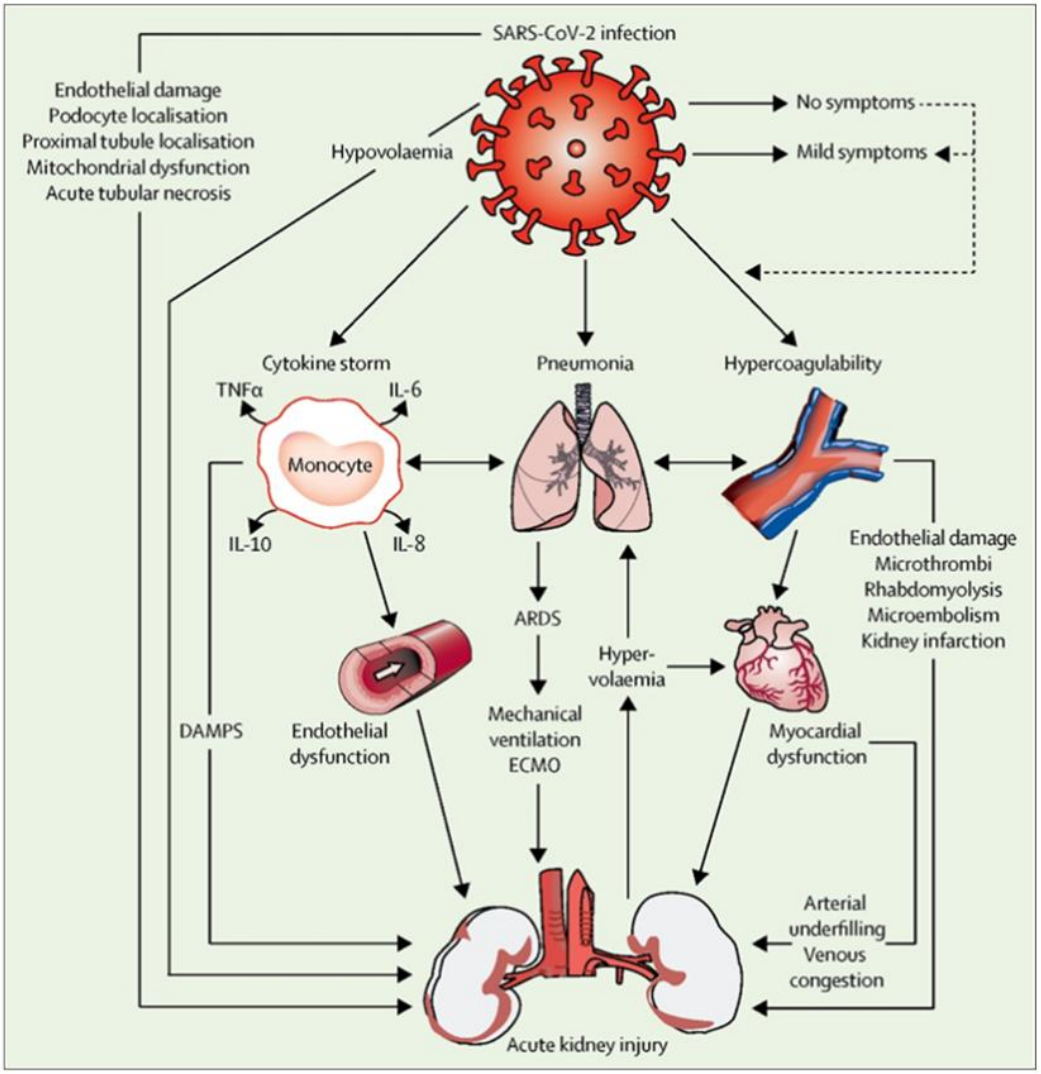

Figure 1. Mechanism of kidney injury in COVID-19

AKI is considered the main manifestation of kidney damage in COVID-19 [21] [22] [23] [26]. High expression of ACE2 in the kidney is observed in the proximal tubules and lesser extent in podocytes. At the same time, ACE2 expression is minimal in the glomerular endothelium and mesangium. This explains the predominant damage to the tubular apparatus of the kidneys and the development of AKI on the type of acute tubular necrosis [2] [21].

Chronic inflammation, increased coagulation activity, impaired immune response, and potential direct damage to the pancreas by SARS-CoV-2 may be one of the underlying mechanisms of the association between diabetes and COVID -19. The proportion of patients with diabetes among patients with COVID-19 ranges from 16.2% in China to 25% in the Russian Federation [12].

China assessed the prevalence of acute kidney injury in patients with COVID-19 and determined the connection between markers of kidney dysfunction and death in patients with COVID-19. The prospective cohort study included 701 patients with COVID-19, 113 (16.1%) of whom died in hospital. On admission, 43.9% of patients had proteinuria and 26.7% had hematuria. Elevated serum creatinine, azotemia and estimated glomerular filtration rate below 60 ml/min/ 1.73 m2 were detected in 14.4, 13.1 and 13.1% of patients, respectively. Acute renal failure developed in 5.1% of patients [2] [22].

Autopsy data from 37 patients with a confirmed diagnosis of COVID-19 aged from 28 to 94 years were analyzed, 35 of them had hypercreatininemia (average 275 μmol/ml) [21] [27]. In all deceased patients, the inflammatory process in the lungs predominated, accompanied by microangiopathy with vascular thrombosis and hemorrhages; angiopathy was also detected in the kidney tissue. All patients had signs of acute damage to the renal tubules of varying degrees of severity, ranging from disruption of the brush border to foci of necrosis of the proximal tubules. The authors suggest that acute damage to the renal tubules during COVID-19 is multifactorial nature – both as a result of hypoxia and right ventricular failure due to pneumonia, and due to a decrease in cardiac output due to left ventricular dysfunction and, accordingly, renal hypoperfusion [21] [26] and this does not exclude the direct effect of SArS-CoV-2 on endothelial cells [24].

On the one hand, the presence of renal pathology is a risk factor for severe COVID-19, and on the other, the development of acute kidney injury in patients with COVID-19 is an independent factor in fatal outcome, regardless of the presence of pre-existing renal disease [22].

In patients without previous kidney damage due to coronavirus infection, both mild renal dysfunction and AKI may develop. According to International Society of Nephrology (ISN), kidney damage is observed in severe course of COVID-19 in 25-50% of cases and is manifested by proteinuria and hematuria, in approximately 15% of cases acute kidney injury develops. According to published data in the USA and Italy, AKI was observed in more than 20% of cases in critically ill patients. In his observations, H. Rabb noted the development of AKI in 5% of hospitalized patients in the general cohort and in 50% of patients in the intensive care unit [21].

Pathogenesis of kidney damage in COVID-19. Numerous pathogenetic mechanisms of kidney damage in patients with COVID-19 can be divided into several groups (Table 1) [25]:

Table 1. The main pathogenetic mechanisms of kidney injury in COVID-19 [25]

Direct cytopathic effect of the SARS-CoV-2 virus on kidney structures	In the kidneys (in podocytes, mesangial cells, parietal epithelium of Bowman's capsule, cells of the proximal tubules and collecting ducts), the receptor for angiotensin-converting enzyme type 2 (ACE2) is expressed for the penetration of the SARS-CoV-2 virus into the cell.
Endothelial dysfunction	SARS-CoV-2 interacts with ACE2 receptors located on the endothelium of blood vessels, causing endothelial dysfunction, which leads to the development of vasoconstriction, vascular hyperpermeability, impaired microcirculation, the development of vascular thrombophilia, multiple microthrombosis and can ultimately cause edema, hemorrhage, necrosis, hemorrhagic infarction of various organs, including the kidneys.
Cytokine storm	Synthesis of a huge amount of pro-inflammatory interleukins (IL-1β, IL-6, tumor necrosis factor, etc.) and chemokines while simultaneously reducing the content of T-lymphocytes in the blood. The developing vicious circle causes destruction of tissue at the source of inflammation, spreading to neighboring tissues and becoming systemic.
Hemodynamic disorders	Right ventricular failure leads to hemostasis in the kidneys, and left ventricular failure leads to a decrease in cardiac output and the development of renal hypoperfusion.
Water metabolism disorders	Hypovolemia can affect the kidneys through a prerenal mechanism. This condition causes renal hypoperfusion and subsequent renal failure. Rhabdomyolysis, metabolic acidosis, and hyperkalemia are also associated with this condition.
Damage to the renin -angiotensin-aldosterone system (RAAS)	Accumulation of angiotensin II and bradykinin causes ARDS, pulmonary edema, myocarditis, and induces vasodilation, causing natriuresis.

The Direct Cytotoxic Effect

The direct cytotoxic effect of SARS-Cov-2 on kidney cells may be the cause of focal segmental glomerulosclerosis, acute tubular necrosis. It has been suggested that glomerular damage occurs and the development of collaptoid glomerulopathy - collapsing focal segmental glomerulosclerosis in patients with dysfunctional APOL1 protein (apolipoprotein 1 - minor apolipoprotein of blood plasma). Light microscopy of kidney specimens from patients who died of COVID-19 revealed increased accumulation of SARS-CoV-2 antigens in renal tubular epithelial cells. By electron microscopy, viral particles of SARS-CoV-2 were localized in the epithelium of proximal

tubules and podocytes. Loss of small podocytes, vacuolization of the cell cytoplasm, and detachment of podocytes from the glomerular basement membrane were noted [21].

Endothelial Dysfunction

Endothelial dysfunction is accompanied by an imbalance of hemostasis with a shift towards the procoagulant side, a decrease in the release of vasodilators and an increase in the release of vasoconstrictor factors and a tendency to spastic reactions in the microvasculature, increased migration of leukocytes through the endothelium with the development of a local inflammatory process.

In COVID-19, endothelial damage and dysfunction most often result from direct entry of the SARS-CoV-2 virus into endothelial cells. Thus, a histological study revealed the presence of fragments of the SARS-CoV-2 virus and apoptotic bodies in the endothelium of the microvasculature of the lungs, myocardium, kidneys, liver and small intestine. Other causes of endothelial dysfunction in patients with COVID-19 may include cytokine storm and immune-mediated damage to endothelial cells. Cytokines and protein proinflammatory mediators are key factors that contribute to endothelial dysfunction. Prolonged exposure to factors leading to endothelial dysfunction contributes to the acquisition of a pro-inflammatory and prothrombotic phenotype by endothelial cells, depletion of the pool of progenitor endothelial cells, which ultimately limits the possibility of restoring its normal phenotype and function [15] [27].

Coagulopathy

The pathogenesis of COVID-19-associated coagulopathy can be illustrated by the age-old concept of Virchow's triad (endothelial dysfunction, hypercoagulability, altered blood flow). Thus, endothelial dysfunction is represented by SARS-CoV-2-induced endotheliitis, immune-mediated activation of endothelial cells, hypoxemia, and increased permeability of the vascular wall. The second component of the triad is hypercoagulation - the formation of NET (Neutrophil extracellular trap), activation of platelets, tissue factor, increased formation of thrombin and fibrins, and a sharp decrease in fibrinolysis. Altered blood flow, in turn, is represented by the formation of pulmonary microthrombosis and microvascular occlusion [15] [23]. Patients suffering from COVID-19 infection show a significant increase in D-dimer levels. Microthrombosis may potentially play an important role in the pathogenesis of organ dysfunction in SARS-CoV-2. Microthrombosis can occur at the level of small arteries in the lungs and in the loops of glomerular capillaries. The high prevalence of thromboembolism of the pulmonary artery with subsequent right heart failure may also contribute to the development of acute kidney injury [12] [21].

Cytokine Storm

In patients with "cytokine storm" syndrome, AKI may develop as a result of increased vascular permeability, intrarenal inflammation, as part of cardiorenal syndrome (CRS) type 1. The latter includes systemic endothelial dysfunction manifested by pleural effusion, edema, intra-abdominal hypertension, third space fluid loss and hypotension. Extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation of the lungs, and continuous RRT may also promote cytokine production [12] [15].

A cytokine storm is a variant of the development of a severe systemic inflammatory response, in which there is a massive recruitment of immune cells to an organ damaged by the virus with the participation of the innate (macrophages, complement system, C-reactive protein, etc.) and adaptive (T- and B-lymphocytes) systems immunity, and the release of a large number of pro-inflammatory cytokines - interleukin (IL)-6, IL-8, tumor necrosis factor-α, monocyte chemotactic protein-1, macrophage inflammatory protein-1A. The acute phase of the disease is characterized by leukocytosis, lymphopenia, increased lactate dehydrogenase, ferritin, D-dimer. In some cases, a delayed and persistent cytokine response occurs, leading to immune damage not only to the lungs, but also to the kidneys [21].

Sporadic autopsy cases and case reports of severe myocarditis with left ventricular systolic dysfunction after COVID-19 suggest the possibility of myocardial infiltration by interstitial mononuclear inflammatory cells. The first manifestations of myocarditis include weakness, increased fatigue, myalgia, and occasionally low-grade fever, which are caused not by myocardial damage itself, but by the manifestation of an infectious-inflammatory process. Sudden cardiac death due to ventricular tachycardia or ventricular fibrillation as a result of myocardial damage in the region of the conduction system of the heart, thromboembolic complications, syncope, cardiogenic shock and acute heart failure are also considered manifestations of myocarditis [26]. Right ventricular failure leads to stagnation of blood in the kidneys, and left ventricular failure leads to a decrease in cardiac output and the development of renal hypoperfusion [12] [21].

RAAS Failure

With age and especially in the presence of hypertension and diabetes, the activity of the main components of the RAAS, including angiotensin II, increases significantly and an imbalance occurs between pro-inflammatory angiotensin 2 and anti-inflammatory angiotensin 1–7. In younger patients, the activity of angiotensin II and angiotensin 1–7 [28], as well as, apparently, ACE and ACE2, remains at normal levels, the balance of vasoconstrictor and inflammatory factors stimulated by angiotensin II, on the one hand, and the formation of oxide nitrogen and blockade of interleukin-6, supported by angiotensin 1–7, on the other hand, preserved. This is one of the factors for a milder course of the disease. However, the gates for the virus to enter are open, which means the morbidity and contagiousness of young patients is high. Elderly patients (over 60 years of age and with concomitant hypertension and type 2 diabetes) have a much more severe course of the disease due to systemic inflammation supported by the predominant activity of ACE and the synthesis of greater amounts of angiotensin II (ACE2),

which is considered the main receptor for SARS-CoV-2 to enter into the cell. In the kidneys, this receptor is located in podocytes, mesangial cells, parietal epithelium of Bowman's capsule, cells of the proximal tubule and collecting duct [2] [21].

SArS-coV-2 can also cause mitochondrial dysfunction, acute tubulonecrosis, vacuole formation due to protein resorption, collapsed glomerulopathy [25] and plasma leakage into the Bowman-Shumlyansky capsule. Another potential mechanism of acute renal tubular injury is connected with the SArS-CoV-2-associated immune response – cytokine storm. The authors also indicate rhabdomyolysis, macrophage activation syndrome, microthrombosis and microembolism due to hypercoagulation and endotheliitis as possible causes of kidney injury [12] [13] [15].

The Connection Between COVID-19 and The Development of Diabetes Mellitus

One of the first published works assessing the relationship between the SARS coronavirus and carbohydrate metabolism is a study conducted in China in 2009. The prospective observation included 39 patients without diabetes and no history of steroid therapy who were hospitalized for laboratory-confirmed coronavirus pneumonia. Twenty of these 39 patients (51%) had hyperglycemia that persisted for several days. Glycemia levels returned to normal by the end of hospitalization in all patients. A re-evaluation of the state of carbohydrate metabolism in these patients was carried out after 3 years. Diabetes was established in only 2 out of 39 people (5%), which confirms the transient nature of glycemia that developed against the background of coronavirus infection, i.e. SH (Steroid hyperglycemia). An immunohistochemical study of biopsies of the lungs, heart, kidneys and pancreas of a 42-year-old patient who died of coronavirus pneumonia was carried out, and ACE2 expression was noted in all organs studied, including the pancreas. Moreover, the level of ACE-2 expression in the cells of the endocrine part was higher than in the exocrine part. Considering the common mechanism of introduction of SARS viruses, we can assume the possibility of hyperglycemia occurring in COVID-19 [23].

4. Discussion

Acute hyperglycemia has been shown to increase ACE2 expression in cells, which may facilitate viral cell entry. However, chronic hyperglycemia, as already noted, reduces the expression of ACE2, making cells vulnerable to the inflammatory and damaging effects of the virus. The interaction between COVID-19 and diabetes may be bidirectional. As noted above, SARS-CoV-2 enters human cells through ACE2. ACE2 is widely expressed in the liver and pancreas, and its deficiency plays a role in the development of insulin resistance and impaired insulin secretion. After endocytosis of the viral complex, ACE2 expression decreases, leading to two types of consequences. First, entry of SARS-CoV-2 into pancreatic islet cells may directly exacerbate beta cell damage. Second, inhibition of ACE2 after viral entry may lead to unopposed angiotensin II production, which impairs insulin secretion. These data suggest that infection may cause the development of diabetes or, at a minimum, severe stress hyperglycemia. The fact that COVID-19 infection causes hyperglycemia in people without pre-existing diabetes has already been documented by some researchers [24].

It is known that diabetes mellitus (DM) complicates the course of many diseases, as it affects almost all systems of the human body [24]. As the practice of 2020 has shown, this phenomenon also applies to infectious diseases [13]. According to WHO recommendations, patients with diabetes are a category of patients at high risk of severe COVID-19. There is information regarding evidence of the cause of the unfavorable course of coronavirus infection in this group of patients [24]. The main argument is the important role of hyperglycemia, which is observed in patients who do not control the course of diabetes [28].

It is known that hyperglycemia causes dilatation of the afferent arterioles of the renal glomeruli, their hyperperfusion and an increase in GFR through mechanisms such as increased synthesis of growth hormone, insulin-like growth factor, glucagon, prostaglandins, nitric oxide. In addition to the listed factors, an increase in GFR is caused by increased synthesis of sorbitol, an increase in extracellular fluid volume with increased secretion of atrial natriuretic peptide, glucosuria, a decrease in insulin levels and other mechanisms that are also a consequence of hyperglycemia. Activation of the intrarenal renin-angiotensin system (RAS) plays an important role in the pathogenesis of DN. Hyperglycemia activates this system (by activating protein kinase C, isoform β2), which is one of the most important mechanisms of damage to the renal microvasculature and the formation of DN.

5. Conclusions

In summary, kidney injury in patients with coronavirus disease is common and can range from proteinuria and hematuria to acute kidney injury, which is associated with high mortality and serves as an independent risk factor for hospital death from all causes in patients with COVID-19. The pathophysiology and mechanisms of kidney injury in patients with COVID-19 are not fully understood and appear to be multifactorial [26]. No specific glomerular pathology was observed in the kidneys during COVID-19. At the same time, acute tubular necrosis was detected in all samples of renal tissue [10] [26]. In patients with SARS-CoV-2 infection, the prevalence of kidney damage is high and usually leads to a poor prognosis, increasing the importance of nephroprotection. New evidence suggests that CKD (Chronic kidney disease) or previous AKI first diagnosed during hospitalization should be recognized as risk factors for severe COVID-19.

Conflict of Interest

The authors declare no conflicts of interest or special funding for the current study.

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